To the editor:

Insufficient evidence to suggest less stringent therapy in hemophilia B?

With great interest we read the article “Comparison of the rates of joint arthroplasty in patients with severe factor VIII and XI deficiency”1 and the comment by Dr Makris, “Is VIII worse than IX?”2 To confirm the hypothesis that severe hemophilia B is clinically milder than severe hemophilia A, Tagariello et al reported a survey of joint arthroplasty in the Italian hemophilia registry IACE. They reported a 3.38-times higher risk of joint arthroplasties in patients with hemophilia A. Based on these findings it was concluded that severe hemophilia B has a milder phenotype than severe hemophilia A and recommended that clinicians plan less primary prophylaxis in patients with hemophilia B.

More cautiously, Dr Makris commented that joint arthroplasty is an end-stage event and can hardly be used as the sole variable to describe the difference between the 2 types of severe hemophilia. A more appropriate variable for this comparison would have been bleeding frequency, but unfortunately these data were not available in the study by Tagariello et al.1

At the van Creveldkliniek, treatment characteristics and bleeding episodes are documented at every routine visit, usually once every 3 to 6 months. Data on surgery and hospitalization are entered directly in the database. We have longitudinal data concerning 5094 treatment-years for 282 patients with severe hemophilia, including 30 patients with severe hemophilia B, born between 1944 and 2008. In this database, orthopedic procedures and parameters of bleeding pattern and treatment were compared across hemophilia type.

In total, 465 orthopedic procedures, including 161 arthroplasties, have been performed. Of 87 patients with severe hemophilia who underwent one or more arthroplasties, 78 had hemophilia A and 9 had hemophilia B; this difference was not statistically significant (Table 1).

The age at onset of joint bleeding is an important indicator of the clinical severity of severe hemophilia.1 In both groups, patients received their first treatment around the age of 1 year. In severe hemophilia A the median age at first joint bleed was 1.9 years, compared with a median of 2.4 years in severe hemophilia B, which was not significantly different due to complete overlap in 5th to 95th percentiles.

Use of prophylaxis was comparable in both groups: 77% in hemophilia A, 73% in hemophilia B. Due to the use of prophylaxis, bleeding frequencies across hemophilia type were quite similar. However, this was not caused by different treatment intensity: annual clotting factor use per kilogram of body weight was also similar across hemophilia type.

In our cohort, onset of bleeding, treatment intensity, and bleeding frequency, as well as the number of arthroplasties, were similar across hemophilia types. Any comparison of hemophilies A and B is hampered by the low numbers of patients with hemophilia B. Therefore, multinational studies are mandatory to answer this question, as was suggested by Lowe and Ludlam.4

Response

Comparing joint arthroplasties in severe hemophilia A with severe hemophilia B

den Uijl and colleagues found that the overall number of joint arthroplasties performed in their patients with hemophilia B (an indirect index of the severity of congenital coagulation disorder) is not different from that in patients with hemophilia A, at variance with our recent report of a significantly less frequent need of these operations in hemophilia B.1 Their conclusions are based on

Table 1. Bleeding pattern, treatment, and outcome according to hemophilia type in patients with severe hemophilia treated at the van Creveldkliniek

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>252 (89%)</td>
<td>30 (11%)</td>
<td>—</td>
</tr>
<tr>
<td>Age at last evaluation, y</td>
<td>27.7 (2.8-51.7)</td>
<td>32.3 (2.5-52.8)</td>
<td>.738</td>
</tr>
<tr>
<td>Arthroplasty</td>
<td>78 (31%)</td>
<td>9 (30%)</td>
<td>.915</td>
</tr>
<tr>
<td>Age at 1st treatment, y</td>
<td>1.1 (0.2-2.7)</td>
<td>1.3 (0.6-2.9)</td>
<td>.065</td>
</tr>
<tr>
<td>Age at 1st joint bleed, y</td>
<td>1.9 (0.5-5.9)</td>
<td>2.4 (0.9-5.5)</td>
<td>.652</td>
</tr>
<tr>
<td>Prophylaxis†</td>
<td>194 (77%)</td>
<td>22 (73%)</td>
<td>.655</td>
</tr>
<tr>
<td>Annual joint bleeding frequency</td>
<td>4.3 (0.3-16.3)</td>
<td>3.8 (0.4-17.8)</td>
<td>.379</td>
</tr>
<tr>
<td>Annual factor use‡</td>
<td>1560 (286-3644)</td>
<td>1260 (302-5826)</td>
<td>.559</td>
</tr>
</tbody>
</table>

Values are reported as numbers (percentages) or medians (5th-95th percentiles).
*Continuous variables were tested with Mann-Whitney test, categorical variables by χ² test.
†Use of prophylaxis was calculated over the last 3 years of treatment.
‡Per kilogram of body weight.

In the meantime, we find no evidence to support the suggestion of less stringent therapy and prophylaxis in patients with hemophilia B.

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References

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